The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery

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INTRODUCTION

Anaemia is defined by the World Health Organization (WHO) as a circulating haemoglobin (Hb) concentration below 130 g/l for men and 120 g/l for women [1]. Anaemia is common and may affect up to one-quarter of the global population, more so in the elderly or those with multiple comorbidities [2]. In the setting of patients undergoing surgery, anaemia is present in a third of all patients [3], but is more prevalent in cardiac surgery and may be present in half of patients [4]. The reasons for this higher prevalence in patients presenting for cardiac surgery are not clear. This may be related to comorbidities, medication or the cardiovascular disease process itself, most commonly atherosclerosis, valvular dysfunction or chronic cardiac failure. A strong association between anaemia and worse outcomes following non-cardiac surgery has been suggested in the literature; however, causation has not been established, and level-one data to support the perioperative treatment of anaemia are lacking [3].

Iron deficiency anaemia is traditionally characterized by the presence of hypochromic, microcytic erythrocytes, reflecting an absolute iron deficiency due to depletion in the body’s iron stores [5]. In many cases of anaemia, particularly in the perioperative setting, a specific aetiology cannot be identified, and patients are often classified as having ‘anaemia of chronic disease’, a diagnosis of exclusion. Anaemia of chronic disease is characterized by the disruption of iron homeostasis initiated by a cytokine-mediated immune response [6, 7]. Increasingly, many cases of anaemia of chronic disease are now recognized to be a functional iron deficiency where normal iron stores are unable to be mobilized for erythropoiesis. In such cases, traditional laboratory red cell indices of mean corpuscular volume, mean corpuscular Hb and ferritin levels may appear normal, but abnormalities may be seen in red cell distribution width [8] or transferrin saturations [9]. Detailed review and guidance on the definition, diagnosis and management for both iron deficiency anaemia and anaemia of chronic disease already exist [6, 7, 9–11]. However, the recognition that perioperative anaemia may, in fact, be due to iron deficiency, which is either absolute or functional, is important as this definition opens the possibility for specific treatment options.

The most rapid and effective method of correcting anaemia is by transfusion of red blood cells. However, blood transfusion itself is not without risk, concerns have arisen over the age of blood used [12] and also that a higher Hb levels may be associated with worse outcomes [13]. In the setting of surgical patients, large database reviews have associated even a single unit of blood transfused with increased morbidity and mortality [14]. Specifically in cardiac surgery, blood transfusion is associated with both infection and ischaemic postoperative morbidity, hospital stay, increased...
early and late mortality and greater hospital costs [15]. On the other hand, prophylactic administration of red blood cells to correct anaemia preoperative in cardiac surgery patients lead to lower rates of intraoperative anaemia and transfusion compared with waiting until the intraoperative period to administer erythrocytes [16].

The treatment of perioperative anaemia using oral iron replacement therapy is, in contrast to blood transfusion, a safe, cheap and relatively convenient therapy [9]. In patients scheduled for colorectal cancer surgery, preoperative oral iron supplementation taken for 2–5 weeks before surgery has been shown to increase preoperative Hb levels and to decrease perioperative transfusion rates [17, 18]. However, the fact that oral iron is absorbed in the duodenum at a rate of only 2–16 mg per day suggests that 3–6 months of oral iron supplementation may be required to completely restore iron stores to normal for anaemic patients [19]. Furthermore, the occurrence of side effects with oral iron (reported in up to half of patients) reduces patient compliance and efficacy [20–23].

Intravenous (IV) iron therapy has been shown to be effective in treating anaemia in a variety of settings: chronic kidney disease, post-partum and preoperative (orthopaedic surgery, colon cancer resections, abdominal hysterectomies and lower limb arthroplasties) [24–32], although many of these studies are observational. Early IV iron preparations using high-molecular-weight dextran were associated with risk of anaphylaxis due to the presence of preformed antibodies in humans to dextran [33, 34]. However, newer preparations are safer, enabling delivery of a full treatment dose in 15 min [34]. Data have successfully shown benefit in improving patient function and quality of life with cardiac failure [9]. However, concern has also been raised that free iron acting as a catalyst may result in increased generation of hydroxyl radicals and oxidative stress, which have been associated with organ damage [35]. Given the high prevalence and likely significance of anaemia in cardiac surgical patients, we performed a systematic literature review of anaemia and outcomes in cardiac surgery, and also the effect of IV iron supplementation therapy in the perioperative period on outcomes following cardiac surgery.

METHODS

Time-frame

The literature search was conducted over the period from January to May 2013. Studies published up to May 2013 were included.

Methodological filters

Four methodological filters were utilized to determine inclusion of studies into the preoperative anaemia and outcome after cardiac surgery literature review. These were (i) study population: the study population was defined as an adult population undergoing any form of open cardiac surgery (excluding transplantation); (ii) preoperative condition: preoperative anaemia, irrespective of the definition of anaemia, or preoperative Hb level was included; (iii) outcome: valid outcomes were morbidity or mortality, not restricted by definition; (iv) language: inclusion was limited to those publications available in English language for ease of interpretation. In addition, the administration of IV iron (pre-, intra- or postoperatively) was added to the criteria for the IV iron use in cardiac surgery review. In the two independent reviews undertaken in this study, papers were not excluded on the basis of sample size, year of study or study design. Case reports were excluded.

Searching for eligible papers

In addition to publication databases [the National Centre for Biotechnology Information (NCBI), Entrez retrieval system (PubMed) and the Web of Science ISI Citation Databases], sources of ongoing and recently completed studies (clinicaltrials.gov, The Cochrane Library of Systematic Reviews) were also interrogated to identify eligible papers.

Keywords searches

The keyword searches undertaken, with no parameter limits defined, were anaemia and cardiac surgery, h(a)emoglobin and cardiac surgery, anaemia and surgery, Hb and surgery, intravenous (and IV) iron and cardiac surgery, and intravenous iron (and IV) and cardiac. The titles and abstracts of each were scrutinized to identify relevant studies fulfilling the review-inclusion criteria.

Backward and forward citation searches

The bibliographies of all relevant studies identified and retrieved were manually searched for additional relevant studies. Furthermore, using the Science Citation Index (Web of Knowledge) papers that have subsequently cited the relevant papers identified from the keyword literature search were reviewed. Publications that had not been previously identified from the primary or backward citation searches were obtained.

Literature analysis

The studies dealing with perioperative administration of IV iron were graded as per the GRADE approach [36]. Study inclusion was determined based on independent review of each of the identified articles by two study investigators (Maurice Hogan and Toby Richards). Once potential studies were judged to be eligible by either reviewer, they underwent full text review by both reviewers working independently and who subsequently compared their judgements. Disagreements were harmonized by consensus and if necessary by arbitration (Andrew Klein).

RESULTS

Overall, 13 studies fulfilling the inclusion criteria, exploring the role of preoperative anaemia or Hb level on outcome after cardiac surgery, were identified. A further three studies were published after the search was completed [37–39], and have been included, so that 16 studies in total are presented (Fig. 1 and Table 1). Four studies (Table 2) were retrieved from an initial search yield of 358 citations investigating the role of IV iron therapy in cardiac surgical patients with perioperative anaemia.
Prevalence of preoperative anaemia in cardiac surgical patients

The true prevalence of anaemia in preoperative cardiac surgery patients depends on the definition of anaemia applied. The WHO definition is itself based on the normal distribution of Hb in the general population. The use of this definition easily facilitates analysis of association between anaemia and outcomes, but as a dichotomous rather than a continuous variable, and consequently the true relevance of having a low Hb level may not always be detected. Studies that applied the WHO definition reported a prevalence range from 15 to just over 54%. The prevalence of 54% is, however, significantly higher than that found by other studies, and the underlying reason is not clear. It may be that, in a tertiary referral centre, many patients are transferred for cardiac surgery and have already stayed in the hospital for a considerable time or be a higher risk with more comorbidities, and this may account for the higher rate reported. One study that defined anaemia as a Hb level less than 125 g/l reported a prevalence of 26% in a patient cohort of 3500 across seven academic hospitals [46]. A single study that looked only at patients aged over 80 years presenting for valve surgery reported an anaemia prevalence of 41% [41]. In general, using the WHO definition, the consensus prevalence of anaemia seems to be around 20–30%, and increases with age and co-existing comorbidities.

Preoperative anaemia and outcomes after cardiac surgery

A summary of the 16 studies identified is provided in Table 1. Although the studies were published between 2002 and 2013, data from 1993 are reported. Only one study was identified that investigated the underlying cause of the anaemia [40]. Mortality, transfusion and length of ICU stay and hospital length of stay were the most common endpoints reported.

Mortality. Mortality rates in anaemic patients varied from 3.1 to 23.8% [45, 52]. The majority of studies reported anaemia to be associated with a higher in-hospital or 30-day mortality rate compared with non-anaemic patients (Table 1). The search for an association between preoperative anaemia and mortality after cardiac surgery lends itself well to retrospective analysis, as almost all cardiac centres have records of preoperative blood tests and also mortality rates. One very important point to consider when interpreting these studies is to try and delineate any outcome effect anaemia may have with the effect of blood transfusion or major bleeding [56]. It is generally well established that patients who receive blood during the perioperative period have higher mortality and greater morbidity than those who do not receive blood transfusion [15].

In isolated coronary artery bypass graft (CABG) surgery patients, a preoperative Hb<100 g/l was associated a significant increase in in-hospital mortality compared with patients with a Hb >100 g/l (17 vs 3.4%). When comparing patients with a Hb <100 vs >100 g/l, the odds ratio (OR) for adjusted in-hospital mortality was 3.17 [45]. This was one of the first studies to look at anaemia and outcome after cardiac surgery, and some of the described practices such as priming the bypass machine with blood, and a transfusion trigger of 100 g/l would not be practiced routinely today.

In another study of isolated CABG surgery patients, it was shown that patients with moderate (<120 g/l in men and <110 g/l in women) and mild anaemia (<120 but <130 g/l in men and >11 but <120 g/l) had a 30-day mortality rate of 6.1 and 4.2%, respectively. Patients with a normal Hb (>130 and <145 g/l in men and >120 and <135 g/l in women) had a mortality of 2.0% at 30 days. High normal Hb levels (>145 and >135 g/l in women) had the lowest mortality rate at 30 days (1.5%) [6]. This study suggests that anaemia has a ‘dose-dependent’ relationship with mortality, and highlights the limitations of using the dichotomous ‘all-or-none’ definition rather than treating anaemia as a continuous variable, when looking for an association. Matsuda et al. [51] reported in an ‘off-pump’ CABG cohort a higher operative mortality rate in anaemic vs non-anaemic patients (1.6 vs 0.3%); however, these results fell on the cusp of statistical significance (P = 0.0501) and were deemed not significant by the authors. Another, retrospective propensity matched study demonstrated a higher operative mortality rate in preoperative anaemic patients vs non-anaemic patients undergoing CABG (12.6 vs 5.2%, respectively) [50]. The literature is, in general, consistent regarding the association of preoperative anaemia and short-term outcomes such as in-hospital or 30-day mortality, and there seems to be a linear relationship between the degree of anaemia and outcomes. However, inconsistencies regarding long-term mortality data have been reported. van Straten et al. [6] showed in 10 025 CABG patients a linear relationship between degrees of a preoperative anaemia and long-term survival (9-year follow-up period). The impact of preoperative anaemia on long-term survival was more pronounced in very low and low Hb patients. The 9-year survival of the moderate and the mild cohort were 37.6 and 56.2%, respectively, compared with 74.7 and 83.4% in the normal and high normal Hb groups, respectively [6].

Carrascal et al. studied 227 cardiac surgery patients requiring cardiopulmonary bypass and failed to identify a relationship between preoperative anaemia and postoperative survival. There...
### Table 1:  Studies of association between anaemia and outcomes after cardiac surgery

<table>
<thead>
<tr>
<th>Author [ref.]</th>
<th>Surgery type</th>
<th>Study design</th>
<th>Sample size</th>
<th>Main outcome analysed</th>
<th>Association between anaemia and main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piednoir et al. [40]</td>
<td>General cardiac</td>
<td>Prospective observational</td>
<td>100</td>
<td>Presence of iron deficiency</td>
<td>Yes (iron deficiency diagnosed in 37% of patients)</td>
</tr>
<tr>
<td>Carrascal et al. [41]</td>
<td>General cardiac</td>
<td>Prospective observational</td>
<td>227</td>
<td>Mortality</td>
<td>Yes (9 vs 18.9%)</td>
</tr>
<tr>
<td>Kulier et al. [42]</td>
<td>CABG</td>
<td>Prospective observational</td>
<td>5065</td>
<td>Cardiac and non-cardiac adverse events</td>
<td>Yes (results stratified according to EuroSCORE)</td>
</tr>
<tr>
<td>van Straten et al. [6]</td>
<td>CABG</td>
<td>Prospective observational</td>
<td>10 025</td>
<td>Mortality (early and late)</td>
<td>Early mortality Yes (hazard ratio 1.48, 95% CI 1.08–2.02; P = 0.013)</td>
</tr>
<tr>
<td>Boening et al. [43]</td>
<td>CABG</td>
<td>Retrospective observational</td>
<td>3311</td>
<td>Mortality</td>
<td>Early mortality Yes (2.2 vs 12.9%, P &lt; 0.001)</td>
</tr>
<tr>
<td>De Santo et al. [44]</td>
<td>CABG</td>
<td>Prospective observational cohort</td>
<td>1214</td>
<td>Acute kidney injury</td>
<td>Yes (adjusted OR 2.06, 95% CI 1.14–3.7)</td>
</tr>
<tr>
<td>Zindrou et al. [45]</td>
<td>CABG</td>
<td>Prospective observational</td>
<td>2059</td>
<td>Mortality</td>
<td>Yes (3.4 vs 17%, P = 0.001)</td>
</tr>
<tr>
<td>Karkouti et al. [46]</td>
<td>General cardiac</td>
<td>Retrospective observational cohort, propensity matched</td>
<td>1030 (propensity matched) 3500 (entire sample)</td>
<td>Mortality</td>
<td>Early mortality, major morbidity, transfusion, ICU LOS Yes (7.5 vs 12.7%, P = 0.014)</td>
</tr>
<tr>
<td>Hung et al. [47]</td>
<td>General cardiac</td>
<td>Prospective observational cohort</td>
<td>2688</td>
<td>Mortality, red cell transfusion, ICU LOS</td>
<td>Early mortality, major morbidity, transfusion, ICU LOS Yes (1.1 vs 3.1%, P = 0.0005)</td>
</tr>
<tr>
<td>Bell et al. [48]</td>
<td>CABG</td>
<td>Retrospective observational</td>
<td>36 658</td>
<td>Mortality</td>
<td>Early mortality Yes (OR 2.37, 95% CI 1.84–3.05; P &lt; 0.0001)</td>
</tr>
<tr>
<td>Cladellas et al. [49]</td>
<td>Valve replacement</td>
<td>Retrospective observational</td>
<td>201</td>
<td>Mortality, major adverse cardiac events</td>
<td>Yes (7.5 vs 17%, P = 0.001)</td>
</tr>
<tr>
<td>Ranucci et al. [50]</td>
<td>General cardiac</td>
<td>Retrospective propensity matched cohort</td>
<td>13 843</td>
<td>Mortality, major adverse cardiac events</td>
<td>Late mortality yes. Results stratified per Hb level</td>
</tr>
<tr>
<td>Elmistekawy et al. [57]</td>
<td>Aortic valve replacement</td>
<td>Interventional cohort study</td>
<td>2698</td>
<td>Mortality</td>
<td>Early mortality no, late mortality yes. Results stratified per Hb level</td>
</tr>
<tr>
<td>Williams et al. [58]</td>
<td>CABG</td>
<td>Retrospective observational</td>
<td>182 599</td>
<td>Mortality</td>
<td>Yes (1.1 vs 3.4%, P &lt; 0.0001)</td>
</tr>
<tr>
<td>Matsuda et al. [59]</td>
<td>CABG</td>
<td>Retrospective observational</td>
<td>1123</td>
<td>Mortality</td>
<td>No (0.3 vs 1.6%, P = 0.0501)</td>
</tr>
<tr>
<td>van Straten et al. [59]</td>
<td>Aortic valve replacement</td>
<td>Prospective observational</td>
<td>1808</td>
<td>Mortality (early and late)</td>
<td>Early mortality no, late mortality yes. Results stratified per Hb level</td>
</tr>
</tbody>
</table>

Mortality (early) refers to 30-day mortality unless otherwise stated. Note: studies did not all apply the same definition of anaemia.

CABG: coronary artery bypass graft; OR: odds ratio; CI: confidence interval; ICU LOS: intensive care unit length of stay.

### Table 2:  Studies examining the effect of perioperative intravenous iron administration in cardiac surgery patients

<table>
<thead>
<tr>
<th>Author [ref.]</th>
<th>Surgery type</th>
<th>Study design</th>
<th>Sample size</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Evidence grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cladellas et al. [52]</td>
<td>Valve surgery</td>
<td>Interventional cohort study</td>
<td>Intervention 75, control cohort 59</td>
<td>Hb levels, blood transfusion</td>
<td>Mortality, MACE (ARF, infection, severe infection, prolonged ventilation)</td>
<td>2C</td>
</tr>
<tr>
<td>Madi-Jebara et al. [53]</td>
<td>General cardiac</td>
<td>Prospective, randomized, double blind study</td>
<td>120</td>
<td>Hb levels</td>
<td>Reticulocyte count, serum ferritin</td>
<td>2C</td>
</tr>
<tr>
<td>Garrido-Martin et al. [54]</td>
<td>Cardiac</td>
<td>Double blind, randomized, placebo-controlled trial</td>
<td>159</td>
<td>Increase in Hb levels</td>
<td>Reticulocyte count and fraction, serum ferritin</td>
<td>2C</td>
</tr>
<tr>
<td>Karkouti et al. [55]</td>
<td>Cardiac or orthopaedic</td>
<td>Double blind, randomized, placebo-controlled trial</td>
<td>31</td>
<td>Increase in Hb levels</td>
<td>A 6-week increase in Hb, reticulocyte count, incidence and volume of red cell transfusion, quality of life</td>
<td>2C</td>
</tr>
</tbody>
</table>

Evidence grade as per GRADE recommendations [36].

ARF: acute renal failure; Hb: haemoglobin; RF: renal failure; MACE: major adverse cardiac events.
was no statistical difference in the survival rates between anaemic and non-anaemic patients (Year 1: 88.2%, Year 2: 81.9% and Year 3: 70.2%) [41]. This is a single-centre study, with relatively low numbers, looking at a specific cohort of patients over 80 years of age. The reported mortality rates were high, at up to 18%.

The study by van Straten highlights again two important issues raised by these association studies: that moderate and mild Hb patients were older and received more red cell transfusions which are confounding factors that may have contributed to the poorer outcomes in these cohorts [6, 41], and further that anaemia is probably best analysed as a continuous variable when looking at its relationship to outcomes.

**Red blood cell transfusion.** Transfusion rates in patients with preoperative anaemia were significantly higher than in non-anaemic patients [43, 45]. Hung et al. [47] reported a 54.1% transfusion rate in anaemic patients compared with 22.4% in non-anaemic patients. Separately, in an observational study of 100 patients undergoing cardiac surgery, iron deficiency, irrespective of Hb level, was associated with a higher transfusion rate compared with non-iron deficient patients (62 vs 35%) [40]. In a retrospective study of 1123 patients undergoing isolated off-pump CABG, anaemia was associated with a higher intraoperative transfusion rate compared with non-anaemic patients (65 vs 22.6%). Postoperative transfusion rates were also higher in the anaemic group (36.2 vs 16.1%) [51]. Two studies failed to identify any association. Carrascal et al. failed to show a significantly raised transfusion rate in preoperative anaemic patients. However, as mentioned above, this may be due to the small sample size and statistical power (n = 227, 42% anaemic patients). Also, differences in Hb between groups were unknown [41].

**Length of stay.** Preoperative anaemia was associated with prolonged ICU length of stay in three studies. De Santo et al. [44] reported that anaemic patients remained in the ICU on average 1 day longer than non-anaemic patients (3.9 vs 2.9 days, P < 0.001), whereas Hung et al. [47] identified that a greater proportion of anaemic patients than non-anaemic patients remained in the ICU for >2 days (19.6 vs 13.7%, respectively). A similar trend reported by Carrascal et al. [41] failed to reach statistical significance (anaemic 7.25 vs non-anaemic 4.95 days, P = 0.069).

Three studies also showed a difference in hospital length of stay between preoperative anaemic and non-anaemic patients. Where an association was identified, anaemic patients stayed between two and four additional days in the hospital than non-anaemic patients [42, 44, 45].

**Other outcomes.** Despite the use of varying outcome definitions, preoperative anaemia, compared with non-anaemia, was associated with a higher incidence of major adverse cardiovascular events and renal complications (including renal failure, dialysis, acute kidney injury and a composite outcome of death and major morbidities) in patients undergoing cardiac surgery [46]. The relationship between anaemia and renal failure is complex, given that chronic renal disease is itself a cause of anaemia, and that the kidneys are among the most sensitive organs to hypoperfusion or reduced oxygen delivery, which may arise due to anaemia. The definition of acute renal failure is also important to consider between studies. Data are conflicting as to whether anaemic patients, compared with non-anaemic patients, have an increased risk of infection or cardiac-only events [41-44, 46]. Furthermore, in patients aged >80 years, a significant independent association between preoperative hypoalbuminaemia and anaemia was identified (OR 2.75, 95% CI 1.05-7.20, P = 0.038) [41].

**Preoperative anaemia and preoperative intravenous iron in cardiac surgery**

Only one trial compared IV vs oral iron therapy in patients undergoing cardiac surgery requiring cardiopulmonary bypass [54]. When comparing IV and oral iron therapy to placebo, no significant differences were found in the three groups concerning transfusion requirements (P = 0.70). Furthermore, at the time of hospital discharge, no differences in Hb were identified in patients who had (P = 0.96) and had not received blood transfusions (P = 0.71). The effects of perioperative oral or IV iron therapy on postoperative transfusion requirements were studied by Garrido-Martin et al. [54], in 159 patients undergoing cardiac surgery. Neither therapy had a significant impact on transfusion rates compared with placebo. Again, the sample size may be inadequate to demonstrate a positive effect. Also, there was only a 5- to 6-day interval between the start of the iron therapy and the operation, which may explain the lack of impact. Cladellas et al. [52] performed an observational cohort study of recombinant erythropoietin in combination with IV iron in patients undergoing valve surgery, and found decreased red cell transfusion, hospital length of stay and better survival in the group treated with combined erythropoietin and iron. The study is small however, and the cohorts were from different time periods.

**Postoperative anaemia and postoperative oral or intravenous iron in cardiac surgery**

One randomized controlled trial was identified which assessed the role of oral iron with or without vitamin C in the setting of acute blood loss anaemia [57]. Irrespective of the treatment group, oral iron supplementation did not aid in restoring postoperative iron storage or red cell mass. However, side effects were commonly reported in the high-dose group (200 mg elemental iron), 62.5% of patients complained of constipation and 86.7% of nausea.

Two randomized controlled trials were identified examining the effect of postoperative IV iron on postoperative anaemia in cardiac surgical patients, although one study used a mixed cardiac and orthopaedic surgical cohort and did not undertake a subspecialty analysis (Table 2) [53, 55]. Overall, Madi-Jebara et al. [53] did not identify a significant difference in subsequent Hb levels or blood transfusion rates using IV iron alone or in combination with recombinant human erythropoietin. However, a randomization bias was observed where the Hb level was significantly higher in the control group (Group I) than in the IV iron alone (Group II) or in combination group (Group III) (108.1 vs 99.5 vs 102.0 g/l, respectively, P = 0.034). This, and the small sample size, could have rendered the increases in Hb, in both treated groups, statistically insignificant. At Day 15, neither group showed a correction in Hb compared with Day 1 (103.3 vs 97.9 vs 101.8 g/l). Although all three groups, and, in particular, the IV iron group, showed a substantial Hb rise on Day 30 (118.7 vs 121.8 vs 124.2 g/l), it was not statistically significant (P = 0.056).

Likewise, Karkouti et al. also observed that administration of postoperative IV iron, either alone or in combination with erythropoietin, did not affect Hb concentration (at 1 week and
6 weeks after surgery), or incidence and volume of red blood cell transfusion (up to 6 weeks after surgery). The length of hospital stay or postoperative quality of life, at either 2 or 6 weeks post surgery, was similarly not affected. However, the combination group did have a significantly higher reticulocyte count on post-operative day 7 (control group 125 vs iron group 121 vs combination group 211, \( P < 0.05 \)) [55], suggesting that the bioavailability of IV iron is indeed superior to oral iron.

**DISCUSSION**

**Prevalence and significance of preoperative anaemia**

This review has highlighted that up to half of cardiac surgery patients are anaemic when they present for cardiac surgery [45, 47]. Preoperative anaemia was found to be independently associated with higher mortality and blood transfusion rate and also longer ICU and hospital length of stay [6, 42–45, 47, 49, 52]. There was variation between studies in the definition of anaemia, and this is important to consider as the significance of the anaemia is likely related not only to its presence but also directly to its severity. Since our literature search, Williams et al. [38] have published an analysis of data on preoperative haematocrit and outcomes of over 180,000 patients collected between 2008 and 2009. They found that preoperative haematocrit is a powerful independent predictor of perioperative mortality as well as renal failure and deep sternal wound infection on patients undergoing isolated primary CABG surgery. They found in their adjusted analyses that every 5-point decrease in preoperative haematocrit was associated with an 8% higher odds of death (OR 1.08; \( P < 0.0003 \)), a 22% increase in the odds of postoperative renal failure (OR 1.22; \( P < 0.0001 \)) and a 10% increase in the risk of deep sternal wound infection (OR 1.10; \( P < 0.01 \)). These results are consistent with the studies we have analysed, and the authors conclude that the next step should be to investigate strategies to increase preoperative haematocrit. Two further studies were also published after our search, both examining the association between anaemia and outcome after aortic valve surgery [37, 39]. Elmistekawy et al. [37] found that anaemia was an independent predictor of both mortality and a composite morbidity in patients undergoing aortic valve surgery, and van Straten et al. [39] concluded that preoperative anaemia was a risk factor for late, but not for early, mortality. This was, however, a retrospective observational, single-centre study which analysed patients between a 12-year time period from 1998 to 2010, and the authors themselves comment that because of a low incidence of overall early mortality, their logistic regression analysis was underpowered.

Conflicting results were observed by Carrascal et al. [41] where no association between preoperative anaemia and postoperative outcome was found. However, this study included only those >80 years of age and was a considerably smaller cohort than in the other studies \( (n = 227) \) and had one of the higher rates of preoperative anaemia (41.9%). Currently the dataset of Williams et al., [38] is by far the largest analysis, whereas the studies presented here represent multiple centres with heterogeneous data series, which may account for variability in reporting and results. Results from the American dataset analysis should be validated in a multicentre homogenous study with power for hard endpoint of survival. Since a combined total of over 250,000 patients were included in studies that did identify an association between preoperative anaemia and postoperative outcome after cardiac surgery, interpretation of Carrascal et al.’s results should be considered carefully.

**Aetiology of anaemia**

Only one small prospective study \( (n = 100) \) was identified that aimed to establish the preoperative prevalence of the most common form of anaemia, i.e. iron deficiency anaemia. In this cohort, 37% of the patients had iron deficiency and of those, 20% were anaemic. No information regarding the cause(s) for non-iron deficiency anaemia in this cohort was mentioned [40]. This subset of iron deficient, but non-anaemic patients represents an interesting and understudied cohort. Indeed in the FAIHR-HF study [9], IV iron was effective in improving patient welfare, heart failure classification and quality of life for patients with absolute or functional iron deficiency independently of baseline Hb. It is logical that these effects may be relevant to cardiac surgery patients. During the peri- and post-cardiac surgery course, the haematopoietic system activates in response to blood loss and anaemia. If there are insufficient iron reserves to allow generation of new red blood cells, then the response will be impaired, and the degree of anaemia worsened or prolonged. It is conceivable that such patients could also benefit from iron supplementation; however, this has not been investigated in surgical patients.

Despite recommendations for preoperative Hb assessment and iron studies so that first-line therapy can be directed to treat the underlying cause of anaemia, the cause of anaemia is rarely defined in cardiac surgical patients [58, 59]. Where the aetiology has been evaluated in this patient group, hospital-acquired anaemia (a non-standard term), iron deficiency anaemia, anaemia of chronic renal disease and anaemia of chronic disease were present in 37.3, 29.3, 10.7 and 7.0% of patients, respectively [58]. Furthermore, postoperative iron studies revealed that the proportion of patients with anaemia of chronic disease or anaemia of inflammation increased to 73.8% at \( \leq 5 \) days and 63.6% between 6 ≤ 10 days after surgery, while only 1.6% (≤5 days) and 3.0% (6 ≤ 10 days) had iron deficiency anaemia (serum ferritin ≤30 µg/l) [59]. However, only 36.5 and 63.5% of patients had pre- and post-operative iron studies, respectively.

**Perioperative intravenous iron treatment**

This review found only one study \( (n = 159) \) reporting on the effect of preoperative iron therapy and the lack of benefit on outcome after cardiac surgery [54]. In light of observations in other surgical settings, it was anticipated that IV iron would achieve improved Hb and a reduction in perioperative blood transfusions, infection rate, length of hospital stay and mortality rate [32, 60–64]. However, no associations with outcome were observed with postoperative IV iron therapy in cardiac surgical patients [53]. In a systematic review of the role of IV iron in patients undergoing non-specific surgery [65], little benefit was found for the use of IV iron. This review was based on only two randomized controlled trials and six observational studies, and they did report a reduction in the proportion of patients requiring transfusion and in the number of transfused units in the observational studies in orthopaedic surgery, but not in cardiac surgery. The authors themselves classify the quality of evidence of these studies as moderate to low [65]. Our conclusions are similar, and although perioperative
administration of IV iron should be expected to treat iron deficiency and thereby correct anaemia in a significant proportion of patients who present for cardiac surgery, this question has not been addressed by appropriately designed studies. The studies of IV iron administration in cardiac surgery patients performed to date represent low quality evidence in our view (Table 2).

Most evidence on IV iron therapy relates to chronic heart failure patients. From data in chronic heart failure patients with iron deficiency, a recently published systematic review and meta-analysis (four randomized controlled trials involving 370 patients treated with IV iron compared with 224 control patients) suggested that IV iron was significantly associated with improved quality-of-life parameters, number of hospitalizations, exercise capacity and mean ejection fraction [66]. Furthermore, only one of the four studies reported an adverse administration reaction, deemed to be mild, and overall IV iron, compared with controls, was associated with less severe adverse events (relative risk 0.43, 95% CI 0.28–0.67, I² = 0%) [9, 66]. Thus, with good safety profiles, better tolerability than oral iron and rapid improvements in Hb level and iron studies, further exploration of the efficacy and effectiveness of preoperative IV iron therapy in cardiac surgical patients is warranted [24, 28, 32, 61, 66].

Blood transfusion is associated with higher health-care resource utilization and increased costs (any transfusion 1.42 times that of non-transfused patients; 111% increase associated with one-unit transfusion compared with non-transfusion) [5, 15, 67–69]. Although cardiac surgery already implements several blood conservation strategies to reduce the need for blood transfusion (for example, cell salvage and use of antifibrinolytic agents), the administration of IV iron to treat preoperative anaemia, if it were proven beneficial, may offer substantial patient and health-care provider benefit [70–72].

The dearth of evidence relating to preoperative anaemia and IV iron therapy in cardiac surgery patients may encourage others to widen the methodological filters in future reviews. One methodological filter was to accept only studies published in the English language. It was considered that this would not be a significant limiting factor to identifying appropriate studies, since English is the language required by internationally recognized journals.

CONCLUSION

In summary, preoperative anaemia is associated with worse outcome after cardiac surgery, which in turn is associated with greater use of health-care resources and higher hospital costs. IV iron therapy has been shown to be beneficial in improving outcome in some patient groups, but there is insufficient evidence in surgical patients, and in particular in cardiac surgery patients, on which to base any recommendations for its use. Appropriately powered randomized controlled trials examining the effect of IV iron on pre- or postoperative anaemia and subsequent outcome after cardiac surgery are required before treatment can be recommended.

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